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(54) Title: PYRROLIDINE SULFONAMIDES

(57) Abstract: The present invention relates to pyrrolidine sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists.

PYRROLIDINE SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to pyrrolidine sulfonamides, pharmaceutical compositions containing them, and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide
- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)
- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2001). Trends Cardiovasc. Med., 10: in press). Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 Jun;155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, and neuromuscular function. Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for pyrrolidine sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of pyrrolidine sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of pyrrolidine sulfonamides for treating conditions associated with urotensin II imbalance.

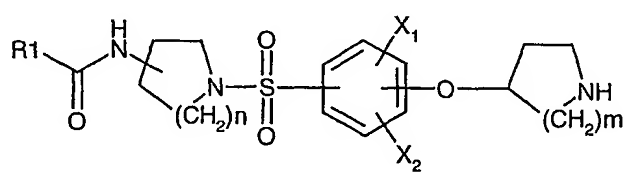
In yet another aspect, this invention provides for the use of pyrrolidine sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, **A-II receptor antagonists,** vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

R_1 is phenyl, furanyl, thienyl, pyridyl, benzofuranyl, naphthyl, benzothiophenyl, benzimidazolyl, indolyl, or quinolinyl, substituted or unsubstituted with one, two or three halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, or methylenedioxy groups;

X_1 and X_2 are hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, CF_3, or CN;

n is 1, 2, or 3;

m is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Preferred compounds are those wherein:

m is 1 or 2;

n is 1,2, or 3;

R_1 is phenyl, substituted or unsubstituted with one or two halogens;

X_1 is hydrogen, 3-bromo, or 3-chloro; and

X_2 is hydrogen or 5-chloro.

Preferred compounds are chosen from the group consisting of:

3,4-Dichloro-N-{1-[4-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-benzamide;

3,4-Dichloro-N-{(R)-1-[3-chloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide;

3,4-Dichloro-N-{1-[3-chloro-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-benzamide;

3,4-Dichloro-N-{1-[3-chloro-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-benzamide;

N-{1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-3,4-dichloro-benzamide;

N-{1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-3,4-dichloro-benzamide;

3,4-Dichloro-N-{(S)-1-[3-chloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide;

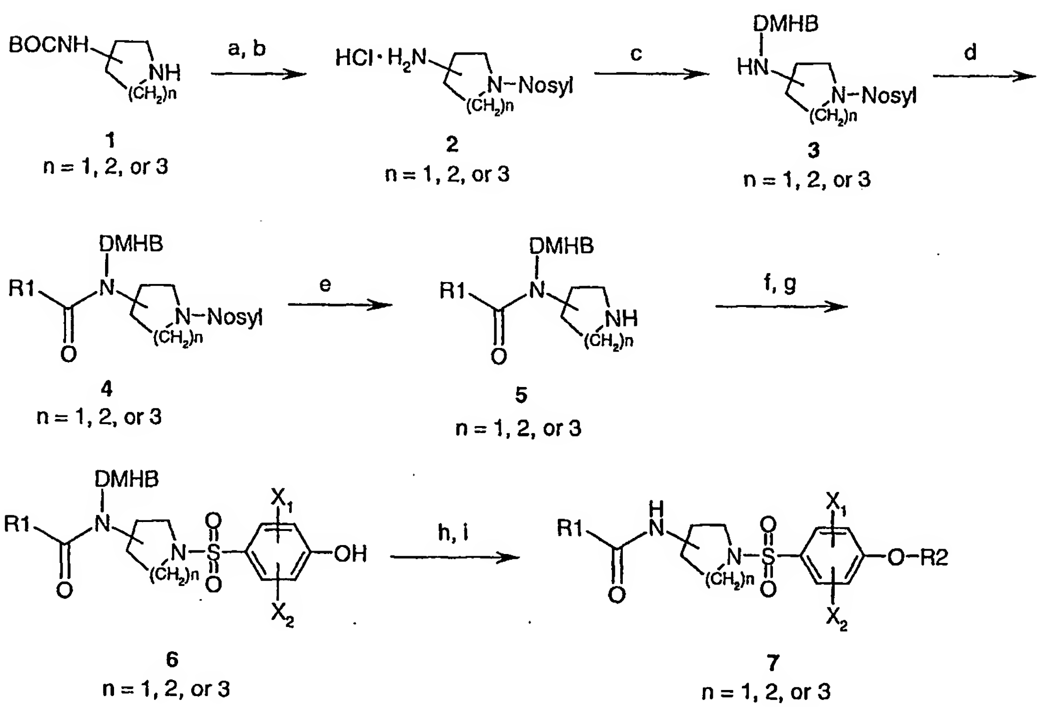
N-{(S)-1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-3,4-dichloro-benzamide;

N-{1-[3-Bromo-4-((S)-pyrrolidin-3-yloxy)-benzenesulfonyl]-piperidin-4-yl}-3,4-dichloro-benzamide; and

3,4-Dichloro-N-{1-[3,5-dichloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-benzamide.

Compounds of Formula (I) may be prepared as shown in scheme 1.

Scheme 1



Conditions: a) 2-nitrobenzenesulfonyl chloride, pyridine, CH_2Cl_2, 0 °C – rt; b) 4 M HCl in 1,4-dioxane, methanol, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), $Na(OAc)_3BH$, diisopropylethylamine, 1% acetic acid in 1-methyl-2-pyrrolidinone, rt; d) R_1COOH, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; e) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; f) $(X_1)(X_2)$-4-hydroxy-benzenesulfonyl chloride, 1,2-dichloroethane, 1-methyl-2-pyrrolidinone, rt; g) potassium trimethylsilanolate, tetrahydrofuran, rt; h) R_2OH, diisopropyl azodicarboxylate, PPh_3, tetrahydrofuran, - 78 °C – rt; i) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

As shown in scheme 1, resin-bound amine **3** was prepared by reductive amination of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with N-nosylated diamine HCl salt **2** which was prepared from (*S*)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester, (*R*)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester, azepan-4-yl-carbamic acid *tert*-butyl ester, or piperidin-4-yl carbamic acid *tert*-butyl ester (**1**). Reactions of resin-bound amine **3** with various benzoic acids resulted in the corresponding resin-bound amides **4**. Amides **4** were treated with potassium carbonate and thiophenol to remove the protecting group and give secondary amines **5**. Sulfonylation of resin-bound amines **5** with various hydroxy-benzenesulfonyl chlorides, followed by treatment with potassium trimethylsilanolate, produced resin-bound phenols **6**. Phenols **6** were then reacted with various alcohols in the presence of triphenylphosphine and diisopropyl azodicarboxylate to give the corresponding resin-bound phenol ethers which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **7**.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example

orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a

pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation and metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, and diabetes.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was

defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^3H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 10 nM – 10000 nM (example 5 Ki = 1500 nM)

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

Preparation of 3,4-Dichloro-N-{(S)-1-[4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide

a) (*S*)-1-(2-nitro-benzenesulfonyl)-pyrrolidin-3-ylamine HCl salt

To a solution of (*S*)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (20.00 g, 107 mmol) in 240 mL of anhydrous methylene chloride at 0 ^{o}C was added 13.03 mL (161 mmol) of anhydrous pyridine, followed by slow addition of 24.99 g (112.7 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt over 1 h and was stirred at rt for 19 h. The mixture was poured into 230 mL of 1 M aqueous $NaHCO_3$ solution. After the resulting mixture was stirred at rt for 30 min, the organic layer was separated and was washed with 175 mL of 1N aqueous HCl solution twice. The resulting organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next step without further purification.

To a mixture of the above residue (33.19 g, 89 mmol) in 33 mL of anhydrous methanol and 33 mL of anhydrous 1,4-dioxane was added 133.5 mL (534 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was stirred at rt for 16 h, concentrated *in vacuo*, redissolved in methanol and concentrated *in vacuo* again. The residue was further dried in a vacuum oven at 35 ^{o}C for 24 h to yield (*S*)-1-(2-nitro-benzenesulfonyl)-pyrrolidin-3-ylamine HCl salt as a yellow solid (30.5 g, 92% over the two steps): ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.56 (s, 3 H), 8.08-7.98 (m, 2 H), 7.94-7.82 (m, 2 H), 3.89-3.79 (m, 1 H), 3.65-3.52 (m, 2 H), 3.43-3.32 (m, 2 H), 2.27-2.14 (m, 1 H), 2.02-1.91 (m, 1 H).

b) 4-Hydroxybenzenesulfonyl chloride

To chlorosulfonic acid (248 mL, 3.37 mol) cooled to –3 ^{o}C was added dropwise a solution of phenol (70 g, 0.744 mol) in 250 mL of anhydrous methylene chloride over a period of 1 hour under argon. The mixture was warmed to rt over 1 h and was stirred at rt for 1.5 h. The mixture was poured over ice, stirred for 30 min, and was extracted with methylene chloride (4 x 2 L). The resulting organic layer was dried over $MgSO_4$ and

concentrated *in vacuo* to yield 4-hydroxybenzenesulfonyl chloride as a sticky brown solid (41.49g, 29%): ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.29-7.38 (d, 2 H), 6.58-6.69 (d, 2 H).

c) 3,4-Dichloro-N-{(S)-1-[4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide

To a mixture of 20.0 g (28.8 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 437.3 mL of 1% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added 26.6 g (86.4 mmol) of (*S*)-1-(2-nitro-benzenesulfonyl)-pyrrolidin-3-ylamine HCl salt and 25.08 mL (144 mmol) of diisopropylethyl amine, followed by addition of 30.52 g (144 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 65 h under argon, the resin was washed with CH_2Cl_2/methanol (1:1, 3 x 400 mL), DMF (3 x 400 mL), CH_2Cl_2 (1 x 400 mL) and methanol (2 x 400 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. Elemental analysis N: 4.56, S: 3.32.

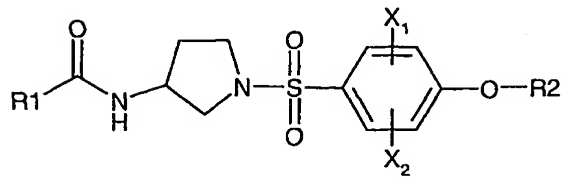
To a mixture of 10 g (10.61 mmol, 1.061 mmol/g) of the above resin in 165 mL of anhydrous 1-methyl-2-pyrrolidinone was added 10.14 g (53.05 mmol) of 3,4-dichlorobenzioc acid and 1.44 g (10.61 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 10.04 mL (63.66 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 44 h, the resin was washed with 1-methyl-2-pyrrolidinone (3 x 150 mL), dichloroethane/methanol (1:1, 3 x 150 mL) and methanol (3 x 150 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 444 $[M+H]^+$.

To a mixture of 200 mg (0.1793 mmol) of the above dry resin in 6 mL of 1-methyl-2-pyrrolidinone was added 248 mg (1.793 mmol) of K_2CO_3 and 0.0985 mL (0.8965 mmol) of PhSH. After the resulting mixture was shaken at rt for 4 h, the resin was washed with methanol (1 x 10 mL), H_2O (3 x 10 mL), methanol (1 x 10 mL), 1-methyl-2-pyrrolidinone (1 x 10 mL), CH_2Cl_2/methanol (1:1, 3 x 10 mL) and methanol (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 517 $[2M+H]^+$, 259 $[M+H]^+$.

To a mixture of 200 mg of the above dry resin in anhydrous dichloroethane/1-methyl-2-pyrrolidinone solution (1:1, 7.5 mL) was added 0.2264 mL (2.799 mmol) of

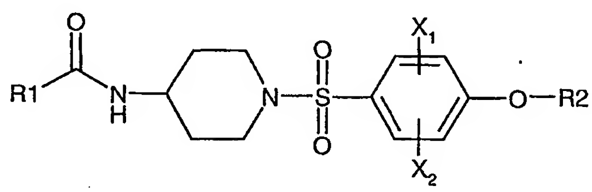
pyridine followed by the slow addition of 0.5393 g (2.799 mmol) of 4-hydroxybenzenesulfonyl chloride. After the resulting mixture was shaken at rt for 96 h, the resin was washed with 1-methyl-2-pyrrolidinone (3 x 10 mL), dichloroethane/methanol (1:1, 3 x 10 mL), dichloroethane (3 x 10mL), methanol (1 x 10 mL), and dichloroethane (2 x 10mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. To a mixture of the dry resin in anhydrous tetrahydrofuran (9.38 mL) was added 0.4713 g (3.674 mmol) of potassium trimethyl silanolate. After the reaction mixture was shaken for 23 h, the resin was washed with tetrahydrofuran (3 x 10mL), 1-methyl-2-pyrrolidinone (2 x 10mL), tetrahydrofuran (3 x 10mL), dichloroethane/methanol (5 x 10 mL), and dichloroethane (3 x 10 mL). An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 415 $[M+H]^+$.

To a mixture of 200 mg of the above dry resin in 8.75 mL of anhydrous tetrahydrofuran was added 443 mg (2.199 mmol) of 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester and 577 mg (2.199 mmol) of triphenylphosphine. After the mixture was cooled to –70 ^{o}C, 433 μL (2.199 mmol) of diisopropyl azodicarboxylate was added to the cold mixture. The resulting mixture was kept at –70 ^{o}C for 30 min while shaking. The mixture was then allowed to warm to 0 ^{o}C over 1 h and shaken at rt for 19 h. The resin was washed with tetrahydrofuran (3 x 10 mL), CH_2Cl_2/methanol (1:1, 10 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 3,4-dichloro-N-{(S)-1-[4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide as a mono-trifluoroacetic acid salt (white powder, 27.7 mg, 27% over 9 steps): MS (ESI) 498 $[M+H]^+$.



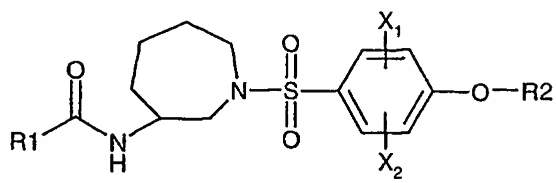
Compounds derived from Scheme 1:

Example	R1	R2	X1	X2	MS (ES+) m/e
2	3,4-dichlorophenyl	piperidin-4-yl	H	H	498 (M+H)
3	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	H	532 (M+H)
4	3,4-dichlorophenyl	piperidin-4-yl	3-bromo	H	577 (M+H)
5	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	5-chloro	566 (M+H)
6	3,4-dichlorophenyl	pyrrolidin-3(S)-yl	H	H	484 (M+H)
7	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	3-chloro	H	518 (M+H)
8	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	3-bromo	H	563 (M+H)



Example	R1	R2	X1	X2	MS (ES+) m/e
9	3,4-dichlorophenyl	piperidin-4-yl	H	H	512 (M+H)
10	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	H	546 (M+H)
11	3,4-dichlorophenyl	piperidin-4-yl	3-bromo	H	591 (M+H)
12	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	5-chloro	580 (M+H)
13	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	3-bromo	H	577 (M+H)

14	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	3-chloro	5-chloro	566 (M+H)
15	3,4-dichlorophenyl	pyrrolidin-3(S)-yl	3-chloro	H	532 (M+H)
16	3,4-dichlorophenyl	pyrrolidin-3(S)-yl	3-bromo	H	577 (M+H)



Example	R1	R2	X1	X2	MS (ES+) m/e
17	3,4-dichlorophenyl	piperidin-4-yl	H	H	526 (M+H)
18	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	H	560 (M+H)
19	3,4-dichlorophenyl	piperidin-4-yl	3-bromo	H	605 (M+H)
20	3,4-dichlorophenyl	piperidin-4-yl	3-chloro	5-chloro	594 (M+H)
21	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	H	H	512 (M+H)
22	3,4-dichlorophenyl	pyrrolidin-3(R)-yl	3-bromo	H	591 (M+H)
23	3,4-dichlorophenyl	pyrrolidin-3(S)-yl	3-bromo	H	591 (M+H)
24	3,4-dichlorophenyl	pyrrolidin-3(S)-yl	3-chloro	H	546 (M+H)

EXAMPLE 25

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

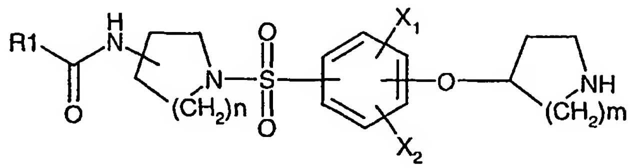
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I) :



Formula (I)

wherein:

R_1 is phenyl, furanyl, thienyl, pyridyl, benzofuranyl, naphthyl, benzothiophenyl, benzimidazolyl, indolyl, or quinolinyl, substituted or unsubstituted with one, two or three halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, or methylenedioxy groups;

X_1 and X_2 are hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, CF_3, or CN;

n is 1, 2, or 3;

m is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

2. A compound Formula (I) of claim 1 wherein m is 1 or 2; n is 1,2, or 3; R_1 is phenyl, substituted or unsubstituted with one or two halogens; X_1 is hydrogen, 3-bromo, or 3-chloro; and X_2 is hydrogen or 5-chloro.

3. A compound of Formula (I) of claim 1 chosen from the group consisting of:

3,4-Dichloro-N-{1-[4-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-benzamide;

3,4-Dichloro-N-{(R)-1-[3-chloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide;

3,4-Dichloro-N-{1-[3-chloro-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-benzamide;

3,4-Dichloro-N-{1-[3-chloro-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-benzamide;

N-{1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-azepan-3-yl}-3,4-dichloro-benzamide;

N-{1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-3,4-dichloro-benzamide;

3,4-Dichloro-N-{(S)-1-[3-chloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-benzamide;

N-{(S)-1-[3-Bromo-4-(piperidin-4-yloxy)-benzenesulfonyl]-pyrrolidin-3-yl}-3,4-dichloro-benzamide;

N-{1-[3-Bromo-4-((S)-pyrrolidin-3-yloxy)-benzenesulfonyl]-piperidin-4-yl}-3,4-dichloro-benzamide; and

3,4-Dichloro-N-{1-[3,5-dichloro-4-(piperidin-4-yloxy)-benzenesulfonyl]-piperidin-4-yl}-benzamide.

4. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrythmias, essential hypertension, pulmonary hypertension, COPD, restenosis, asthma, neurogenic inflammation metabolic vasculopathies, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, neuromuscular function, or diabetes.